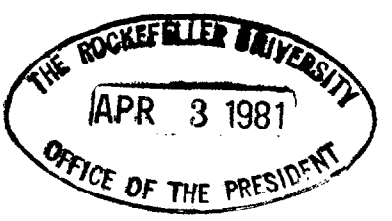
Duke University Medical Center
DURHAM, NORTH CAROLINA
27710



DEPARTMENT OF PHYSIOLOGY
BOX 3709

TELEPHONE (919) 684-2262

March 27, 1981

Dr. Joshua Lederberg, President
The Rockefeller University
1230 York Avenue
New York, NY 10021

Dear Dr. Lederberg:

Many thanks for your enquiry about the effects of magnesium sulfate. Although, as you remarked, my own work concerned its effects in the central nervous system, not on peripheral tissues, I will try to give you a reasonable opinion, even if unsupported by data.

A high concentration of a magnesium salt may well have a local anesthetic effect, for divalent cations raise the threshold of excitation of all excitable tissues. Soaking broken skin in a hypertonic solution may raise the subcutaneous concentration sufficiently to block excitation of nerve endings. It would not be too difficult to set up an experiment to check whether this is true. In principle, I would not mind doing it myself, except that at the moment I am committed to other projects. You mention the supposed effect of hypertonicity per se. It is a time-honored, though possibly not rigorously proven clinical tradition, that hypertonic solutions reduce the oedema of inflammation. In Amsterdam we were taught to use sodium bicarbonate or carbonate, because the alkalinity was believed to help control infection. With the use of antibiotics, the latter may not be important anymore. Since procaine and its relatives are not always tolerated, there may be some reason to use a magnesium salt for its combined hypertonic and local anesthetic effect. Whether it has an additional specific anti-inflammatory action by some effect on capillary permeability, or on reactive tissue cells, I am in no position to judge.

Then there is the use of intravenous magnesium sulfate in the treatment of eclampsia of pregnancy. I have often wondered whether our work make this therapy obsolete. For the following reasons I am not so sure: (1) As you have read in our 1966 paper, when we received a rather massive dose of this compound we did not go to sleep, but there was a noticeable sedative effect. When we measured magnesium uptake in tissues (Amer. J. Physiol. 214:406, 1968), we found that some did enter the brain and spinal cord, although uptake in CNS was much less than in other organs. However, in the light of our later work on cellular excitability changes (J. Neurobiol. 1: 181 and 197, 1969), the small rise of magnesium ion concentration achieved by intravenous administration may be sufficient to becalm the hyperexcitability of a preeclamptic brain. (2) It may be that in the preeclamptic state, the blood-brain barrier is abnormally permeable to magnesium, and thus the concentration achieved in brain may be higher than

expected. (3) Magnesium has additional effects, which include vasodilatation (Viveros & Somjen, Experientia 24: 457, 1968) and diuresis, both desirable in the treatment of eclampsia.

To answer your question, then, whether magnesium sulfate should be removed from the Pharmacopeia , my advice would be to study it again, after some decades of neglect, by modern methods, and in direct comparison with more recent drugs. Such a simple compound could have advantages in some cases, or it may be entirely obsolete. It would not be possible to decide this without well-designed clinical trials. I am afraid that few obstetricians are fully aware of the various points of view enumerated in the previous paragraph. Renewed investigation followed by appropriate publicity and entry into current textbooks could be beneficial.

I have left magnesium as a research topic about twelve years ago, but after having been preoccupied with other matters, we recently began a study of the permeability of the blood-brain barrier to calcium ions. We intend to measure concurrently ion activity in circulating arterial blood, and in the interstitial fluid of the central nervous system, with ion-selective electrodes (for brain tissue we use microelectrodes). We have made measurements in the two components (blood and brain) separately, and will soon put them together in the same animal. From calcium it should be a short step to magnesium, if and when magnesium-selective ion exchanger will become available, and then we will be able to answer your questions more directly. Meanwhile we will be kept busy solving the equally puzzling and clinically important problems of calcium-deficiency tetany, and of the central effects of hypercalcemia.

This letter grew excessively long, but I would also like to ask a question myself. I have advance information that my NIH grant renewal will probably end up in the bin marked "approved but not funded". Would you know of an agency/foundation/fund that may be interested in sponsoring our clinically relevant study of ion exchanges between blood and central nervous system? If this is an inappropriate question to be addressed to you, I must apologize, but I feel compelled to explore every possibility.

Yours very sincerely,

George Somjen

George G. Somjen, M.D.
Professor of Physiology

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